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(51) Int.Cl. ⁵ C07D 487/04; C07D 519/00; A61K 31/495; A61K 31/535

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Imidazopyridazines

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Germany (Federal Republic of) ;

(30) (DE) P 43 39 868.5 1993/11/23

(57) 8 Claims

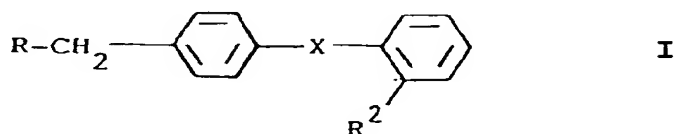
Notice: This application is as filed and may therefore contain an
incomplete specification.



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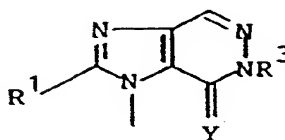
Abstract of the Disclosure

Novel imidazopyridazine derivatives of formula I



wherein

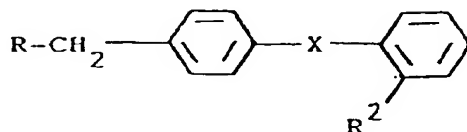
R is



and R^1 , R^2 , R^3 , X and Y are as defined in Patent Claim 1, and their salts, exhibit antagonistic properties towards angiotensin II and can be used for the treatment of hypertension, aldosteronism, cardiac insufficiency and increased intraocular pressure, and of disorders of the central nervous system.

Patent Claims

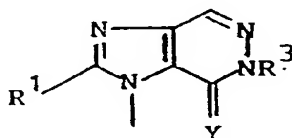
1. Imidazopyridazine derivatives of formula I:



I

wherein

5 R is



- R^1 is A, alkenyl or alkynyl each having up to 6 C atoms, C_3 - C_7 -cycloalkyl- C_kH_{2k} - or C_1 - C_6 -alkyl, wherein a CH_2 group is replaced by O or S,
- R^2 is H, COOH, COOA, CN, NO_2 , NH_2 , $NH-COR^4$, $NH-SO_2R^4$ or 1H-tetrazol-5-yl,
- R^3 is a C_1 - C_{10} -alkyl, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl group which is mono- to tetrasubstituted by C_3 - C_8 -cycloalkyl, CN, COOH, COOA, Ar, Het¹, Het², $-CO-R^5$, $-CO-Ar$, $-CO-Het^2$, $-CO-NR^6R^7$, $-CO-R^8$, $-C(=NR^9)-A$, $-C(=NR^9)-Het^2$, NO_2 , NR^6R^7 , $-NR^{11}-COR^5$, $-NR^{11}-COAr$, $-NR^{11}-COOA$, $-NR^{11}-SO_2R^5$, $-NR^{11}-SO_2Ar$, OR^{10} , $-S(O)_m-A$, $-S(O)_m-Ar$, $-SO_2-NH-Het^2$, $-SO_2-OR^{11}$, Hal and/or 1H-tetrazol-5-yl and in which a CH_2 group can also be replaced by an O or S atom; or unsubstituted C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl,
- R^4 and R^5 are each C_1 - C_5 -alkyl, in which one or more H atoms can also be replaced by F,
- R^6 and R^7 are each H, A, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl, Ar, ArC_nH_{2n} - or Het²,
- R^6 is also $-CH_2COOA$, $-SO_2-A$ or $-SO_2-Ar$,
- R^6 and R^7 together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het², $-CO-Ar$, $-COOA$,

- CO-N(A)₂, -CH₂OH, -SO₂-Ar and/or -NH-CO-A and/or interrupted by O or by -NR¹²-,
- 5 R⁸ is -NH-CHR¹¹-COOH, -NH-CHR¹¹-OOA, -CH₂S(O)_m-Ar, -CH₂C-COOA, -C_nH_{2n}-NO₂, -C_nH_{2n}-NR⁶R⁷ or -C_nH_{2n}-NH-COOA,
- R⁹ is H, OH, CN, R¹³, OR¹³ or OAr,
- R¹⁰ is H, C₁-C₁₀-alkyl which can be substituted by Ar, Het², COA or COAr, or is Ar, COA, COAr or CONR⁶R⁷,
- R¹¹ is H or A,
- 10 R¹² is H, A, Ar, COOA, Het² or SO₂Ar,
- R¹³ is A, C₂-C₆-alkenyl or C₂-C₆-alkynyl,
- X is absent or is -NH-CO-, -CO-NH-, -O-CH(COOH)-, -NH-CH(COOH)-, -NA-CH(COOH)-, -CH=C(COOH)-, -CH=C(CN)- or -CH=C(1H-tetrazol-5-yl)-,
- 15 Y is O or S,
- A is C₁-C₆-alkyl,
- Ar is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R⁵, OR⁵, COOH, COOA, CN, NO₂, NH₂, NHA, N(A)₂, NR¹¹-COR⁵, NR¹¹-COAr¹, NR¹¹-SO₂R⁵, NR¹¹-SO₂Ar¹, Hal or 1H-tetrazol-5-yl,
- 20 Ar¹ is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R⁵, OR⁵, COOA or Hal,
- Het¹ is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or =NR⁹ and/or whose ring N atom(s) can in each case be substituted by A or Ar,
- 25 Het² is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or monosubstituted or disubstituted by A,
- 30 Hal is F, Cl, Br or I,
- k is 0, 1, 2, 3 or 4
- 35 m is 0, 1 or 2 and
- n is 1, 2, 3, 4, 5 or 6,
- and their salts.
2. a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

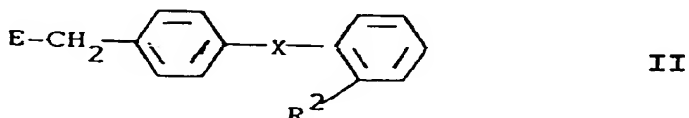
d]pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6- α -isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R² is as defined in Claim 1,

is reacted with a compound of formula III:

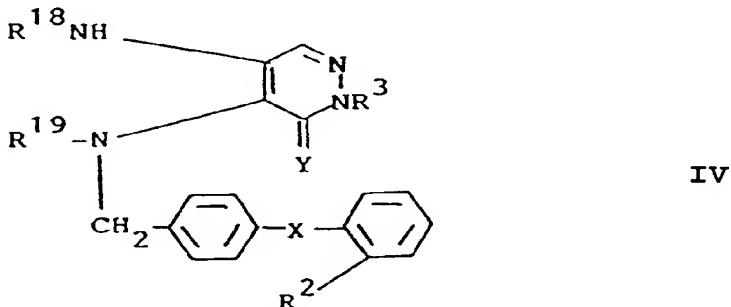


wherein

R is as defined in Claim 1,

or

(b) a compound of formula IV:



wherein

R^{14} is R^1 -CO or H,

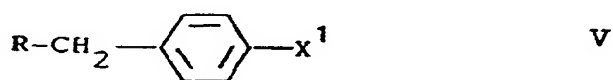
R^{15} is H (if R^{14} is R^1 -CO) or R^1 -CO (if R^{14} is H), and

R^1 , R^2 , R^3 , X and Y are as defined in Claim 1,

5 is treated with a cyclizing agent,

or

(c) to prepare a compound of formula I wherein X is -NH-CO- or -CO-NH-, a compound of formula V:

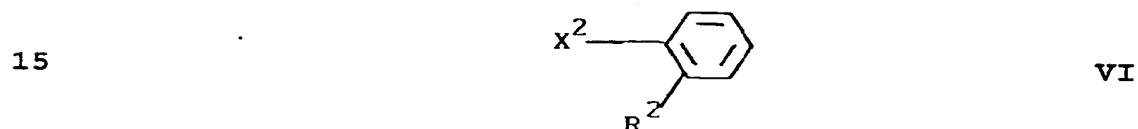


10 wherein

X^1 is NH_2 or $COOH$, and

R is as defined in Claim 1,

or a reactive derivative of this compound, is reacted with a compound of formula VI:



wherein

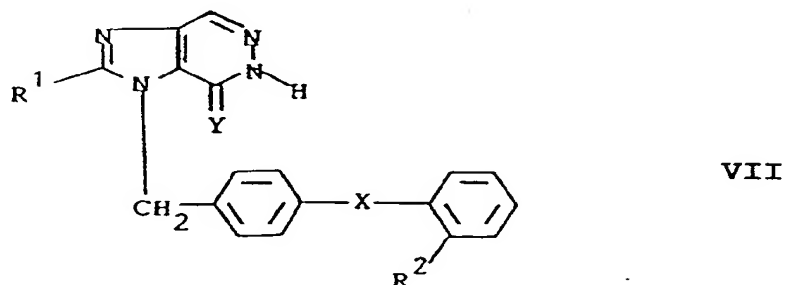
X^2 is $COOH$ (if X^1 is NH_2) or NH_2 (if X^1 is $COOH$), and

R^2 is as defined in Claim 1,

or with a reactive derivative of this compound,

20 or

(d) a compound of formula VII:



wherein

R^1 , R^2 , X and Y are as defined in Claim 1,
is reacted with a compound of formula VIII:



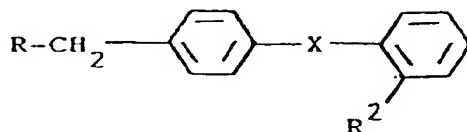
VIII

wherein

- 5 R^3 and E are as defined above,
or a reactive derivative of such a compound,
or
(e) to prepare a compound of the formula I which contains
a $-C(=NR^9)-$ group, a corresponding carbonyl compound is
10 treated with a compound of the formula H_2N-R^9 , wherein R^9
is as defined in Claim 1, or
(f) a compound of formula I is freed from one of its
functional derivatives by treatment with a solvolysing or
hydrogenolysing agent,
15 and/or in that one or more radicals R and/or R^2 in a
compound of formula I are converted to one or more
different radicals R and/or R^2 , and/or a base or acid of
formula I is converted to one of its salts.
4. Process for the preparation of pharmaceutical
20 formulations, characterized in that a compound of formula
I according to Claim 1, and/or one of its physiologically
acceptable salts, are incorporated into a suitable dosage
form together with at least one solid, liquid or semi-
liquid excipient or adjunct.
25 5. Pharmaceutical formulation, characterized in that
it contains at least one compound of formula I according
to Claim 1, and/or one of its physiologically acceptable
salts.
6. Compound of formula I according to Claim 1, and
30 its physiologically acceptable salts, for the control of
diseases.
7. Use of compounds of formula I according to Claim
1, and/or their physiologically acceptable salts, for the
preparation of a drug.
35 8. Use of compounds of formula I according to Claim
1, and/or their physiologically acceptable salts, in the
control of diseases.

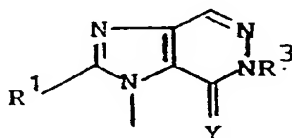
Patent Claims

1. Imidazopyridazine derivatives of formula I:



wherein

5 R is



- R^1 is A, alkenyl or alkynyl each having up to 6 C atoms, C_3 - C_7 -cycloalkyl- C_kH_{2k} - or C_1 - C_6 -alkyl, wherein a CH_2 group is replaced by O or S,
- R^2 is H, COOH, COOA, CN, NO_2 , NH_2 , $NH-COR^4$, $NH-SO_2R^4$ or 1H-tetrazol-5-yl,
- R^3 is a C_1 - C_{10} -alkyl, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl group which is mono- to tetrasubstituted by C_3 - C_8 -cycloalkyl, CN, COOH, COOA, Ar, Het¹, Het², $-CO-R^5$, $-CO-Ar$, $-CO-Het^2$, $-CO-NR^6R^7$, $-CO-R^8$, $-C(=NR^9)-A$, $-C(=NR^9)-Het^2$, NO_2 , NR^6R^7 , $-NR^{11}-COR^5$, $-NR^{11}-COAr$, $-NR^{11}-COOA$, $-NR^{11}-SO_2R^5$, $-NR^{11}-SO_2Ar$, OR^{10} , $-S(O)_m-A$, $-S(O)_m-Ar$, $-SO_2-NH-Het^2$, $-SO_2-OR^{11}$, Hal and/or 1H-tetrazol-5-yl and in which a CH_2 group can also be replaced by an O or S atom; or unsubstituted C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl,
- R^4 and R^5 are each C_1 - C_5 -alkyl, in which one or more H atoms can also be replaced by F,
- R^6 and R^7 are each H, A, C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl, Ar, ArC_nH_{2n} - or Het²,
- R^6 is also $-CH_2COOA$, $-SO_2-A$ or $-SO_2-Ar$,
- R^6 and R^7 together are also an alkylene chain having 2-5 C atoms, which can be monosubstituted or polysubstituted by carbonyl oxygen, Ar, Het², $-CO-Ar$, $-COOA$,

- CO-N(A)₂, -CH₂OH, -SO₂-Ar and/or -NH-CO-A and/or interrupted by O or by -NR¹²-,
- 5 R⁸ is -NH-CHR¹¹-COOH, -NH-CHR¹¹-OOA, -CH₂S(O)_m-Ar, -CH₂C-COOA, -C_nH_{2n}-NO₂, -C_nH_{2n}-NR⁶R⁷ or -C_nH_{2n}-NH-COOA,
- R⁹ is H, OH, CN, R¹³, OR¹³ or OAr,
- R¹⁰ is H, C₁-C₁₀-alkyl which can be substituted by Ar, Het², COA or COAr, or is Ar, COA, COAr or CONR⁶R⁷,
- R¹¹ is H or A,
- 10 R¹² is H, A, Ar, COOA, Het² or SO₂Ar,
- R¹³ is A, C₂-C₆-alkenyl or C₂-C₆-alkynyl,
- X is absent or is -NH-CO-, -CO-NH-, -O-CH(COOH)-, -NH-CH(COOH)-, -NA-CH(COOH)-, -CH=C(COOH)-, -CH=C(CN)- or -CH=C(1H-tetrazol-5-yl)-,
- 15 Y is O or S,
- A is C₁-C₆-alkyl,
- Ar is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R⁵, OR⁵, COOH, COOA, CN, NO₂, NH₂, NHA, N(A)₂, NR¹¹-COR⁵, NR¹¹-COAr¹, NR¹¹-SO₂R⁵, NR¹¹-SO₂Ar¹, Hal or 1H-tetrazol-5-yl,
- 20 Ar¹ is an unsubstituted phenyl group or a phenyl group monosubstituted or disubstituted by R⁵, OR⁵, COOA or Hal,
- Het¹ is a five- or six-membered saturated heterocyclic radical having 1 to 3 N, O and/or S atoms, which can be monosubstituted by carbonyl oxygen or =NR⁹ and/or whose ring N atom(s) can in each case be substituted by A or Ar,
- 25 Het² is a five- or six-membered heteroaromatic radical having 1 to 3 N, O and/or S atoms, which can also be fused with a benzene or pyridine ring and/or monosubstituted or disubstituted by A,
- 30 Hal is F, Cl, Br or I,
- k is 0, 1, 2, 3 or 4
- 35 m is 0, 1 or 2 and
- n is 1, 2, 3, 4, 5 or 6,
- and their salts.
2. a) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-benzyl-7-oxo-1H-imidazo[4,5-

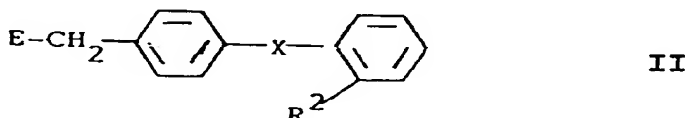
d]pyridazine and its potassium salt;

b) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6- α -isopropoxycarbonylbenzyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt;

c) 1-(2'-(1H-Tetrazol-5-yl)biphenyl-4-ylmethyl)-2-butyl-6,7-dihydro-6-N,N-dimethylcarbamoylmethyl-7-oxo-1H-imidazo[4,5-d]pyridazine and its potassium salt.

3. Process for the preparation of imidazopyridazines of formula I according to Claim 1, and their salts, characterized in that

(a) a compound of formula II:



wherein

E is Cl, Br, I, a free OH group or an OH group which has been functionally modified to acquire reactivity, and

R² is as defined in Claim 1,

is reacted with a compound of formula III:

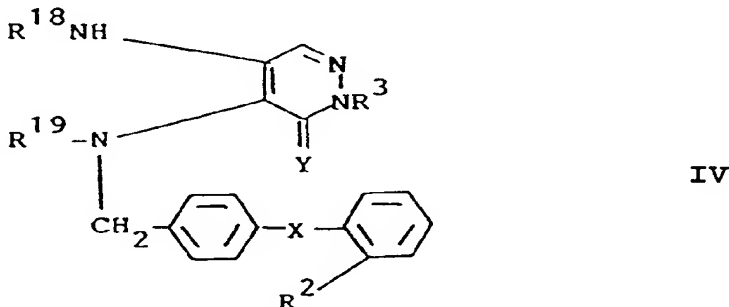


wherein

R is as defined in Claim 1,

or

(b) a compound of formula IV:



wherein

R^{14} is R^1 -CO or H,

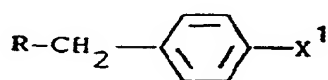
R^{15} is H (if R^{14} is R^1 -CO) or R^1 -CO (if R^{14} is H), and

R^1 , R^2 , R^3 , X and Y are as defined in Claim 1,

5 is treated with a cyclizing agent,

or

(c) to prepare a compound of formula I wherein X is -NH-CO- or -CO-NH-, a compound of formula V:



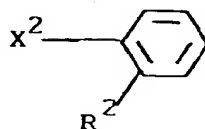
V

10 wherein

X^1 is NH_2 or COOH, and

R is as defined in Claim 1,

or a reactive derivative of this compound, is reacted with a compound of formula VI:



VI

15

wherein

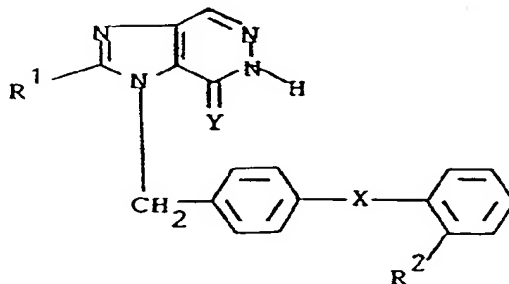
X^2 is COOH (if X^1 is NH_2) or NH_2 (if X^1 is COOH), and

R^2 is as defined in Claim 1,

or with a reactive derivative of this compound,

20 or

(d) a compound of formula VII:



VII

wherein

R^1 , R^2 , X and Y are as defined in Claim 1,
is reacted with a compound of formula VIII:



VIII

wherein

- 5 R^3 and E are as defined above,
or a reactive derivative of such a compound,
or
(e) to prepare a compound of the formula I which contains
a $-C(=NR^9)-$ group, a corresponding carbonyl compound is
10 treated with a compound of the formula H_2N-R^9 , wherein R^9
is as defined in Claim 1, or
(f) a compound of formula I is freed from one of its
functional derivatives by treatment with a solvolysing or
hydrogenolysing agent,
15 and/or in that one or more radicals R and/or R^2 in a
compound of formula I are converted to one or more
different radicals R and/or R^2 , and/or a base or acid of
formula I is converted to one of its salts.
4. Process for the preparation of pharmaceutical
20 formulations, characterized in that a compound of formula
I according to Claim 1, and/or one of its physiologically
acceptable salts, are incorporated into a suitable dosage
form together with at least one solid, liquid or semi-
liquid excipient or adjunct.
25 5. Pharmaceutical formulation, characterized in that
it contains at least one compound of formula I according
to Claim 1, and/or one of its physiologically acceptable
salts.
6. Compound of formula I according to Claim 1, and
30 its physiologically acceptable salts, for the control of
diseases.
7. Use of compounds of formula I according to Claim
1, and/or their physiologically acceptable salts, for the
preparation of a drug.
35 8. Use of compounds of formula I according to Claim
1, and/or their physiologically acceptable salts, in the
control of diseases.